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Review

Pathophysiologic changes due to TASER® devices versus excited delirium: Potential relevance to deaths-in-custody?

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ABSTRACT

The syndrome of excited delirium has been implicated in some deaths-in-custody which also involved the use of electronic control devices (ECDs) (including those manufactured by TASER International) on subjects. This review is an update on recent studies of pathophysiologic changes related to these two separate but parallel topics: a) first, the use of ECDs during law-enforcement activities; and b) second, the occurrence of excited delirium during such activities. This is a narrative review of elements that may be of use in generating hypotheses relating to potential similarities or differences between the two topics. Differences between changes in most factors due to excited delirium versus those of ECD applications were not readily apparent in most cases. These factors include: direct and indirect effects on the cardiovascular system, respiration, rhabdomyolysis and muscle enzymes, hyperkalemia, acidosis, hyperglycemia, and increased hematocrit. One factor that may exhibit consistent differences, however, is increased body temperature, which is often evident during excited delirium (versus a lack of increase temperature during ECD exposures). Thus, on the basis of this review, a more detailed delineation of this factor could be a major focus for future forensic investigations of deaths-in-custody involving either excited delirium or ECD exposures.

1. Introduction

"Electronic control devices" (ECDs) (such as those manufactured by TASER International [Scottsdale, Arizona, USA]) have been implicated in some deaths-in-custody (reviewed previously in this journal).[1] The syndrome referred to as "excited delirium," however, is one possible explanation for some of these deaths. Since that first review in this journal (completed three years ago), additional research studies, using both animals and human subjects, have been completed in several laboratories. The purpose of the current review is to provide an update on the two parallel topics ([a] the use of ECDs, and [b] the occurrence of excited delirium), and to provide additional insights into possible improvements in pathological examinations of these deaths. This is a narrative review of elements that may be of use in generating hypotheses relating to potential similarities or differences between the two topics.

Because extreme applications of ECDs to experimental human subjects cannot reasonably be performed, some of the data included in this review are from studies of anesthetized animals. Most of the human studies of ECD exposures were supported by TASER International and involved shorter-duration exposures than some cases of deaths-in-custody reported to be possibly associated with use of the devices.

2. Is "excited delirium" a valid term?

Four components are usually considered to be necessary for a definition of the excited delirium syndrome: a) delirium with agitation, b) respiratory arrest, c) hyperthermia, and d) death.[1] Although some have referred to excited delirium as a "non-medical term,"[2] it is a valid general description of a syndrome, prior to further determination of an underlying diagnosis.[3] Excited delirium can be considered a heterogeneous condition, with multiple variant types that could differ in both presentation and clinical course. The syndrome is properly defined as a physical state for which several underlying diagnoses are feasible,[4,5,6] with cocaine-induced excited delirium perhaps the most common variant. Although certain clinical cases may be consistent with this sub-type, expert witnesses in some legal cases have suggested that the term "cocaine-induced excited delirium" would not be valid without respiratory arrest and death.[7] In other instances, some behavioral symptoms may be similar to those observed in psychiatric conditions such as catatonia.[8] These cases, however, are not

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necessarily classified, *per se*, as excited delirium. Detweiler et al.[9] noted that, when a subject exhibits an increasing degree of catatonic features, delirious mania may convert to a malignant catatonic state, particularly in the presence of hyperthermia. (Also see additional discussion in section "*7. Body temperature*" below.)

As DiMaio and DiMaio[10] pointed out, the fact that excited delirium is not a billable procedure (listed by the American Medical Association) does not mean it is not a valid diagnosis. The authors pointed out that the National Association of Medical Examiners has recognized excited delirium as a valid entity for a number of years. In addition, the American College of Emergency Physicians formally recognized the syndrome recently.[11]

3. Hyperkalemia

3.1. Hyperkalemia during ECD experiments

As mentioned in the previous review,[1] increased blood potassium concentration ($[K^+]$) was noted in an animal model (*Sus scrofa*) after repeated or long-duration ECD exposures. In subsequent experiments, performed with the same methods of anesthesia and physiological measurements,[12,13,14] other repeated or long-duration ECD applications also resulted in significant hyperkalemia immediately after exposure. The most extreme hyperkalemia (mean value of 7.6 mEq/l) was seen after 3 min of cycled (7 s on/3 s off) applications of the TASER® X26 ECD.[12] ("TASER" is a registered trademark of TASER International. "X26" is a trademark of TASER International.) Within 30 min, however, potassium had returned to a normal level. There were no significant differences in pre-exposure blood $[K^+]$ from survivors versus non-survivors.

Valentino et al.[15,16,17] reported no significant change in blood $[K^+]$ for up to 30 days post-exposure in swine due to applications of an Aegis ECD. The same group of investigators,[18] however, found that two 40-s applications of a TASER X26 ECD resulted in a significant increase in blood $[K^+]$ at 5 min post-exposure. In another series of 40-s X26 ECD applications, succinylcholine was administered to swine to prevent acidemia due to muscle contraction.[19] Fatal ventricular fibrillation (VF) occurred in only one animal out of eight exposed to two applications. The authors reported no blood potassium values outside a normal range in their experiments.

In experiments of human volunteers, there were no significant changes in venous blood $[K^+]$ after 5-s applications of the TASER X26 ECD.[20] Ho et al.[21] found no significant changes in serum $[K^+]$ after 15-s TASER X26 "drive stun" applications in human volunteers. These experiments were funded by TASER International. Longer exposure periods were not investigated.

Even though muscle contraction responses to ECD applications would typically bypass volition, the overall responses may be similar to changes during exercise.[22] Due to these similarities, knowledge of prior studies of exercise/muscle contraction may be useful in understanding responses during ECD applications. Blood $[K^+]$ will increase to a greater extent in untrained human subjects than in exercise-trained subjects.[23] In addition, after exertion, trained subjects recover to resting concentrations of plasma potassium more quickly.[24] Knochel et al.[23] hypothesized that such subjects may be able to avoid potentially dangerous hyperkalemia via biologic adaptation of skeletal muscle cells. Whether or not exercise-trained subjects are better able to tolerate long-duration exposures to ECDs is unknown. Since most muscles would become inactive immediately after an ECD discharge is discontinued, a rapid uptake into the muscle (similar to what may happen after cessation of exercise[25]) may help prevent any harmful level of extended hyperkalemia.

Hyperkalemia can occur in association with hyperglycemia.[26] (See section "*8.2. Increased blood glucose after ECD applications or excited delirium*" below, for further discussion relative to ECD applications or excited delirium.) Hyperkalemia is a potentially severe complication of rhabdomyolysis (which may occur after repeated muscle contractions) (also see additional discussion in section "*5. Rhabdomyolysis and muscle enzymes*" below), and could result in life-threatening arrhythmias.[27] In addition to release of potassium by muscle, other factors can play a role in changing blood potassium during muscular exercise. For example, the liver can exchange potassium actively due to activation of adrenergic receptors,[28] which could arise due to increased catecholamines.

Although severe hyperkalemia can occur in some patients without major electrocardiographic manifestations,[29] profound effects on cardiac conduction (as specifically reflected in the electrocardiogram) usually result.[30] Efforts to use quantitative criteria to define effects of hyperkalemia on cardiac conduction have been difficult to validate in humans.[31] In swine, an increase in T-wave amplitude does not usually happen until blood $[K^+]$ reaches a level of about 7.6 mEq/L.[32] In the previous ECD study in which blood $[K^+]$ reached that level,[12] T-wave elevation was not noted. Cardiac arrest will usually take place at a level of 12 mEq/L.[33] Blood $[K^+]$ may not be predictive of hemodynamic instability in any individual patient, since the effects will depend on both the rate of increase and associated metabolic factors, including the pH.[34]

3.2. Hyperkalemia during excited delirium

Some deaths after cocaine use (without concurrent exposure to ECDs) have been related to severe hyperkalemia (e.g., see Parks et al.[34]). This aspect may be of interest in selected cases of deaths occurring after excited delirium. In spontaneously breathing pigs (without any ECD applications), administration of cocaine resulted in an increase in blood $[K^+]$ from 3.9 mEq/L pre-infusion to 6.5 mEq/L 2 h after start of infusion.[35] The authors, however, suggested that "respiratory depression and resulting hypoxemia and acidosis were the primary reasons for cardiac arrest" in the animals. As in ECD experiments,[12] changes in respiration and acidosis (rather than hyperkalemia) may also have been more important factors relating to death during excited delirium. (Also see additional discussion in section "*6. Respiration, acidosis, and blood lactate*" below.)

In cases of life-threatening hyperkalemia in humans due to methamphetamine[36] or cocaine,[37] blood $[K^+]$ levels were 8.5 and 8.9 mEq/L, respectively. In one recent case of rhabdomyolysis due to 3,4-methylenedioxy-N-methylamphetamine (MDMA, "ecstasy"), hyperkalemia (blood $[K^+]$ of 9.4 mEq/L) was noted as the cause of death.[38] Since drug abuse is often present in cases of excited delirium (or, additionally, ECD usage), these associations should be considered. (Also see additional discussion in section "*9. Additional information regarding drug abuse*" below.)

4. Direct and indirect effects of ECDs or excited delirium on the cardiovascular system

4.1. ECDs

Using human subjects in experiments funded by TASER International, Ho et al.[39] reported no detectable changes in 12-lead electrocardiograms due to 15-s TASER X26 ECD exposures immediately after an exhaustive exercise regimen. In another study of up to 5-s X26 device applications, the exposures appeared "to be safe and well tolerated from a cardiovascular standpoint."[40] Heart rate and mean blood pressure were increased slightly but significantly. Vilke et al.[41] also reported increased heart rate, but no changes in ventilatory parameters, after 5-s X26 ECD exposures. Dawes et al.[42] found no cardiac capture in ten volunteer subjects exposed to 5-s X26 ECD discharges, with the probes actually fired into the chest

region (and not simply taped to conductive gel, as in previous studies of humans). After 10-s applications of a "new generation" ECD manufactured by TASER International, there were no apparent electrocardiogram changes of any importance.[43] (In experiments of an earlier preliminary prototype version of the device,[43] one subject demonstrated rapid ventricular capture for the duration of the discharge.) These last two studies mentioned above[42,43] were funded by TASER International. The findings may not apply to situations of ECD applications of longer durations or with repetitive discharges.

In arrest-related deaths occurring in persons who collapsed less than 15 min after ECD application and in whom rhythm was documented, asystole or pulseless electrical activity was the rhythm primarily found.[44] The findings of rhythm analysis are a necessarily small group and the sample size is worthy of caution. While none of the 8 subjects who collapsed (while actually on a cardiac monitor) demonstrated VF, one other subject's demise was one of the first recorded cases of VF potentially induced by ECD application.

Investigators have presented convincing evidence that, under certain selected conditions, ECD applications can result in ventricular capture (and associated mechanical contraction) in an anesthetized swine model.[18,19,45] Whether different anesthetics play a role in such responses is unknown (see Jauchem[46] for discussion of such potential effects). In addition, there is controversy regarding the appropriateness of a swine model for studying susceptibility to arrhythmias, with some researchers affirming this idea (reviewed by Jauchem[46–47]) and others disputing it.[48] Ho et al.[49] reported that ECD applications resulted in greater atrial and ventricular irritability in methamphetamine-intoxicated Dorset sheep (*Ovis aries Dorset*) of small body weight. Despite these findings, cardiac events such as VF are still unlikely to occur, in most cases, as a result of any direct effect of ECD pulses on the heart.[50] There was no VF in animals that expired after extreme ECD exposures,[12] but rather respiratory arrest with organized QRS electrical activity. Thus there was possibly pulseless electrical activity. (When such activity does occur, it may change spontaneously to asystole.[51]).

Cevik et al.[52] suggested an ECD "application does not have an acute direct effect on cardiac function but causes a final sympathetic surge from the central nervous system." Although not based on any data of any specific research studies on the topic, Holden et al.[53] speculated that, independently of any primary electrical effect of ECDs, arrhythmias may be caused by exercise- or stress-induced catecholamine release. Hyperkalemia, in combination with high catecholamine levels, could actually facilitate cessation of VF and, therefore, be protective.[54] (Also see additional discussion in section "*10. The potential combination of factors*" below.)

Michaud and Dupuis[55] hypothesized that "the sudden tetanic muscular contractions" induced by ECDs "represent a high level of mechanical energy that is nothing less than a severe blunt trauma," which could result in dysrhythmias due to "commotio cordis." (Coincidentally, a swine model is appropriate for studying such a cause of dysrhythmia.[56])

In experiments of 30- or 60-s ECD applications in pigs,[13] detectible levels of cardiac troponin I were present in only one out of ten animals. Ho et al.[21] reported that all types of troponins measured were <0.2 ng/ml immediately, 8 h, and 24 h after TASER X26 "drive stun" applications in human volunteers. VanMeenen et al.[57] also found no detectable levels of cardiac troponin I, in a group of 99 law-enforcement officers and trainees, 24 h after 5-s X26 ECD exposures.

4.2. Excited delirium

Roberts[58] noted "previous reports have documented PEA/asystole rather than ventricular tachycardia or fibrillation" in "patients with cocaine-induced delirium who suffered sudden unexpected cardiac arrest." Since cocaine is often present in subjects exposed to ECDs during law-enforcement incidents,[1] this is an important observation. Long-term cocaine use, however, is necessary for the development of cardiac myofibrillary alterations.[59] In persons aged 18-45, more than ten uses of cocaine significantly increases the risk of myocardial infarction, particularly in younger persons.[60] While myofibrillary changes may not be seen on pathology until after long-term cocaine use, the clinical effect of cocaine and coronary insufficiency are seen early in young and seemingly healthy people with no other risk factors.[61] Concomitant use of cigarettes and alcohol potentiates the cardiac risks of cocaine.[62]

5. Rhabdomyolysis and muscle enzymes

5.1. ECDs

In experiments of 30- or 60-s ECD applications in pigs,[13] serum myoglobin was increased significantly immediately after exposure and at all sampling points in a 3-h post-exposure period. In another series of cycled applications (7 s on/3 s off) of the X26 ECD,[12] serum myoglobin was also increased significantly immediately after exposure and at most sampling points post-exposure. The maximum value (76 ng/ml), however, was less than half that which occurred in a study of healthy men performing isometric or isokinetic exercise.[63]

Sanford et al.[64] presented two cases of men with rhabdomyolysis after exhibiting violent behavior and receiving TASER X26 ECD applications. One of the subjects had received six ECD applications and had a serum myoglobin of 169 ng/ml.The other subject (after only a single ECD shock) exhibited a peak creatine phosphokinase (CPK) of 8086 units. As Ho and Dawes[65] pointed out, however, the relative contributions of physical struggle versus ECD applications in cases of this nature have not been determined. Other investigators have found that exhaustive muscle contractions (e.g., 50 maximal contractions of elbow flexor muscles[66]) result in large increases in blood CPK.

Significant increases in serum total CPK and in the CPK-MM fraction have occurred after 30- or 60-s ECD exposures,[13] and even after only three 5-s applications of a TASER X26 ECD,[67] to anesthetized swine. Sloane and Vilke[68] suggested that increases in CPK would not be surprising after ECD application, since massive contraction of muscle could cause such changes. On the basis of pooled data from several different studies of humans (a meta-analysis funded by TASER International), Dawes et al.[69] reported no clinically significant changes in CPK after ECD exposures (in contrast with the X26 ECD results in animal studies). The vast majority of the human studies, however, involved only a single 5-s application. It is unknown whether longer applications to humans would result in clinically significant rhabdomyolysis.

5.2. Excited delirium

Although verified cases of strictly-defined excited delirium in conjunction with rhabdomyolysis were not studied, the most recent report of rhabdomyolysis due to licit or illicit drugs was by Tóth and Varga.[70] Drugs included amphetamine, cocaine, alcohol, MDMA, heroin, and methadone. Berrens et al.[71] presented a case of rhabdomyolysis caused by D-lysergic acid diethylamide.

6. Respiration, acidosis, and blood lactate

6.1. ECDs

Respiration is dependent on a "bellows" mechanism via the action of the abdominal wall, diaphragm, intercostal muscles, and accessory muscles of respiration.[72] During ECD applications, each of

these could be affected. Gill[73] suggested that prolonged ECD applications could cause respiratory problems. Studies of ECD effects on respiration were reviewed previously.[47] A lack of effective respiration, which was seen in anesthetized animals, has not been replicated in experiments of human subjects. Dawes et al.,[74] however, noticed in prior studies "that subjects often held their breath for the first 5–7 s due to a pain response" to ECD exposure. Human studies are limited by the need to include healthy individuals in clinically-controlled research settings. In some studies, the subjects may have been aware of the need to actively focus on breathing.[75]

Vilke et al.[20] found a doubling of arterial blood lactate concentrations in human subjects exposed to a single 5-s application of the X26 ECD. Other similar studies have been reviewed previously.[47] In a study of ethanol-intoxicated subjects,[76] a 15-s TASER X26 ECD discharge resulted in a greater rate of increased blood lactate (and decreased pH) than during the pre-exposure period. Ho et al.[77] reported that a 15-s exposure to the X26 ECD did not worsen acidemia that was already present in anaerobically exhausted human subjects, although there was a slight increase in blood lactate. In another study,[78] a similar ECD exposure did not appear to worsen acidemia in exhausted subjects any differently than continued exertion. (These last three studies mentioned above were funded by TASER International.) The investigators noted that their data may not apply to situations of ECD applications of longer durations or repetitive discharges. Lactic acidosis resulted from exposures to an ECD marketed for civilians ("TASER C2") in experiments of both human[79] and animal[14] subjects. Although some investigators may consider acidosis to be "a life-threatening condition regardless of the underlying condition,"[80] short ECD applications may cause only very transient decreases in blood pH.

6.2. Excited delirium

Whether asphyxia is associated with excited delirium is uncertain. Byard et al.[81] have reviewed studies pertinent to this question. Hypoxia, even in anesthetized animals (i.e., without the perception of pain), could trigger a rapid stress reaction, leading to the release of both epinephrine and norepinephrine into the blood. Some postmortem findings associated with asphyxia are nonspecific.[72] In cases of asphyxiation, blood levels of epinephrine and norepinephrine can increase immediately at death.[82] Hirvonen et al.[83] determined that increased postmortem blood concentrations of catecholamines could be used as indicators of hypoxia, with the caveat that levels could rise in a short period after death. Takeichi et al.[82] reported that epinephrine may gradually decrease, while norepineprhine may increase further, due to release postmortem from cardiac sympathetic nerves. All of these results may be heavily confounded by other events that increase catecholamine levels independently from asphyxia, i.e., stress, agitation, exercise, acidosis, and a host of other issues that could be concomitant. Acidosis can directly stimulate release of epinephrine from the adrenal medulla.[84] (Also see section "*10. The potential combination of factors*" below.)

7. Body temperature

No significant increases in body temperature were found after extreme applications of the TASER X26 device[12] or after 30-s applications of the TASER C2 ECD[14] using an animal model. Lim and Seet[85] were surprised, considering the vulnerability of nervous tissue to thermal injury, that neurological effects were not reported more frequently after ECD exposures. Although Bui et al.[86] recently reported neurological sequelae of ECD applications, these were not thermal in nature. In a population-based study of 426 ECD activations by law-enforcement personnel,[87] only one death was subsequently attributed to hyperthermia.

Hyperthermia is a pivotal issue in discussions surrounding excited delirium, since the presence of hyperthermia in a state of excited delirium is considered a harbinger of death.[88] As Bunai et al.[89] noted, "Although the findings associated with hyperthermia" during excited delirium "are nonspecific, they are useful in diagnosing hyperthermia when combined with reconstruction of the scene of death." The most recent report of a case of cocaine-induced excited delirium, concurrent with hyperthermia, was by Menaker et al.[90] An increase in body temperature at time of death could be caused by a variety of factors, including physical activity, emotional stress, intoxication due to illicit drugs, and hyperthyroidism.[91] Each of these may be relevant to excited delirium. (Also see section "*11.5 Hyperthermia*" below.)

8. Additional topics not discussed in previous review: Increases in hematocrit and blood glucose

8.1. Increased hematocrit after ECD applications or excited delirium

In one ECD study of swine, non-survivors exhibited a significantly higher pre-exposure hematocrit than survivors.[12] In all previous[67,92] and subsequent[13,14] ECD experiments in which hematocrit was measured, the value also increased significantly after exposure. The mechanisms of these changes in hematocrit have not been determined, but potential candidates have been reviewed previously.[93] These include: a) increased capillary hydrostatic pressure due to effects of muscle contraction on venules (with plasma fluid pushed into the extravascular space); b) release of metabolic waste products from muscles (with increased osmolality of the interstitial space); and c) splenic contraction.

Potential detrimental effects of acutely-increased hematocrit (and related hemorheological alterations[94]) include problems with tissue perfusion, and reduced venous return and cardiac output due to higher viscosity.[93] Although polycythemia increases blood oxygen content, this potential benefit may be counterbalanced by a decrease in cardiac output, which will, in turn, adversely affect pulmonary diffusion and alveolar ventilation.

In a study of 53 human subjects exposed for 10 s to a particular ECD (the same model as mentioned in another reference[43] above), there was no change in mean hematocrit.[95] Changes of hematocrit in humans exposed to long-duration or repeated applications of ECDs, however, have not been studied. Unfortunately, since hematocrit values increase rapidly after death,[96] a forensic investigation of this phenomenon would be problematic. On the basis of the information presented above, however, the clinical implications of increased hematocrit could be serious. In addition, although there have been no published reports of autopsy findings of hypercoagulability or clot-related demise after ECD applications, acute muscle contraction (even without increased hematocrit) can result in increased thrombotic tendency,[97] with sustained platelet and coagulation hyperactivity.[98] Acute muscle contraction can result in both prothrombic and hypofibrinolytic responses.[99] Any such detrimental effects, however, would appear intuitively to be dependent on a high level of either long-duration or repetitive ECD applications. Low degrees of muscle contraction may not have such effects.

Cocaine can cause a transient increase in hematocrit in humans, due to splenic contraction.[100] If a subject has pre-existing polycythemia from this or other causes (e.g., an endocrinopathy[101]), ECD application could exacerbate the situation. Although, in rare cases, fatalities that include cocaine-associated rhabdomyolysis may be associated with disseminated intravascular coagulation,[102] such a process would likely occur only after some time period,

e.g., during the occurrence of renal failure.[103] Thus it is unlikely that ECD applications would be related to any cases of disseminated intravascular coagulation.

8.2. Increased blood glucose after ECD applications or excited delirium

In previous experiments,[12–14,67,92] significant increases in blood glucose were observed either immediately after or within 30 min after ECD applications. In the study of the most extreme ECD applications,[12] blood glucose increased significantly in non-survivors, but not in animals that survived. These results were consistent with Asadollahi et al.,[104] who noted significantly higher mortality in critically-ill human patients with plasma glucose levels greater than an upper cut-off value of 125 mg/dL (which was identical to the mean value of blood in animals that survived ECD applications in the previous study by Jauchem et al.[12]). In a more recent study, polytraumatized human patients exhibited greater mortality with higher blood levels of glucose[105] compared with normoglycemic individuals. It should be noted, however, that other factors during critical illness and trauma may have no bearing on situations involving deaths-in-custody.

In some acute pathophysiological states, combinations of several different blood factors may be important. For example, hyperglycemia and hyponatremia together may have a cumulative effect on mortality.[104] In experiments with significant increases in blood glucose after ECD application,[12,13,14,67,92] however, hyponatremia occurred in only one study.[67] Hyperglycemia may result in decreased erythrocyte deformability,[106] which can occur concurrently with increased hematocrit.[93]

It is unknown whether increased blood glucose is a function of physical struggle, excited delirium, drug intoxication, or ECD applications during law-enforcement situations. Alcohol,[107] opioids, and opioid analogs[108] can, by themselves, result in hyperglycemia. (Also see additional discussion in section "*11.3 Hyperglycemia*" below.)

9. Additional information regarding drug abuse

Although deaths due to cocaine occur only in a minority of subjects who use the substance, it is toxic over a large range of blood concentrations.[109] Elevated catecholamines could increase the toxicity of cocaine.[110] Pilgrim et al.[111] confirmed earlier results of Karch et al.[112] of no correlation between blood methamphetamine and outcome. The authors[111] suggested that femoral blood be taken so that artifacts due to postmortem redistribution could be diminished. They noted that amphetamine-class drugs either caused or exacerbated pre-existing cardiovascular disease. Karch[59] explained that pathological changes in the heart (sometimes seen after excited delirium) due to methamphetamine or cocaine usually require chronic use of the drugs over long periods of time.

Each of the potential effects of factors discussed in the previous sections can be exacerbated by recreational use of cocaine, methamphetamine, or alcohol. Sudden deaths while in custody are nearly always associated with the presence of positive drug levels.

10. The potential combination of factors

Predicting the effects of any given ECD exposure or excited delirium scenario (alone or in combination with each other) is complicated. The combination of acidosis, hyperkalemia, and elevated adrenergic activity may result in antagonism that offsets any harmful effects of an individual factor.[113] O'Neill and Paterson[114] suggested that, although hyperkalemia and increased circulating catecholamines individually may each be harmful, there could actually be a *beneficial* interaction between these changes if they are concurrent. For example, during exercise, catecholamines may modulate calcium currents in the heart, and thereby help to protect it from hyperkalemia.[115]

Deaths during law-enforcement custody have been likened to a "perfect storm" of severe physiologic conditions including a hyperactive stress response potentiated by restraint, physical exertion, or drug use.[116] In this situation, prior health problems may be unmasked. (It is unknown, however, whether ECD exposure would exacerbate any pre-existing conditions.) For example, polycythemia (or associated changes) (also see section "*8.1. Increased hematocrit after ECD applications or excited delirium*" above) could be present during apprehension of unlawful subjects. Potential causes (prior to any use of an ECD) include psychological stress, endocrinopathy, diabetes, chronic alcohol abuse, cocaine use, or use of opiates.[93] There is also an increased lethality of cocaine when used in combination with heroin, opiates, and alcohol.[109]

11. Possibilities for future forensic investigations

11.1. General concepts

If some of the pathologic changes outlined above have not been specifically investigated, they each cannot be assumed to have *not* been present. Even if such changes are found, they may be taken out of context when considering the whole situation. There are few solutions for elucidating causes of deaths-in-custody. Some of the points below, however, may provide ideas for future investigations.

11.2. Blood catecholamines

Blood should be drawn from the subclavian or femoral vessels to prevent postmortem redistribution of drugs from tissues into blood, which could result in elevated levels as artifacts.[117] If a relatively long period of time has elapsed, blood obtained at the beginning of admission to a hospital (if available) could still be valuable for toxicologic analysis.[118]

High levels of catecholamines in the circulation could lead to hyperthermia and increased metabolism. If these changes are not apparent on autopsy, a lack of findings could occur in some cases of deaths-in-custody.[119] Often, no blood samples are available immediately after cases of excited delirium.

Postmortem levels of blood catecholamines may be related to the magnitude of stress responses in individuals.[120] Elevated levels of catecholamines postmortem in vitreous humor and cerebrospinal fluid could be associated with a long-lasting stress reaction,[121] such as that occurring during excited delirium.

11.3. Hyperglycemia

Epinephrine simultaneously enhances hepatic glucose production and inhibits glucose clearance.[122] Increased sympathetic drive during ECD exposures or excited delirium may be important in causing increases in blood glucose. Zilg et al.[123] suggested that, since blood glucose levels decrease rapidly postmortem, vitreous humor glucose alone should be used to determine hyperglycemia. Possible postmortem changes such as redistribution and hemoconcentration, however, should be considered.[124]

11.4. Inherited ion channelopathies

After some deaths-in-custody, postmortem analysis for inherited ion channelopathies[125] could be considered. With recent advances in molecular technology, examination of cardiac-channel

factors may provide a potential pathogenic basis for unexplained deaths.[126–127] Examination of myocardial contraction band necrosis potentially due to acute use of drugs (e.g., MDMA),[128–129] would also be of particular interest.

11.5. Hyperthermia

Since hyperthermia is often evident during excited delirium (versus a lack of increased temperature during ECD exposures), a major focus for new forensic investigations may involve this factor. By examining dopamine dysregulation biomarkers in the brain postmortem, and by analyzing induction of heat shock protein, Mash et al.[88] found that death likely occurs in conjunction with hyperthermia during excited delirium. Concentrations of dopamine transporters have been below a normal range in all excited delirium cases in which such levels have been examined.[130] Isolated increases in serum creatinine levels may be useful in investigations of death due to hyperthermia,[131] which often includes absent or nonspecific findings at autopsy.[132] In addition to these factors, other aspects or markers that may distinguish excited delirium hyperthemic effects from ECD effects (i.e., events that occur with hyperthermia but probably *not* with ECD applications alone) include: elevated cardiac troponin T in left and right heart blood, external iliac blood, pericardical fluid,[133] and cerebrospinal fluid[134]; elevated urea nitrogen, creatinine, and uric acid in pericardial fluid[135]; elevated calcium (but decreased magnesium) in pericardial fluid[136]; decreased adrenocorticotropic hormone in cerebrospinal fluid[137]; increased ubiquitin immunoreactivity in midbrain periaqueductal gray matter[138]; elevated mast cell tryptase in serum[139]; increased ratio of serum/cerebrospinal chromogranin A[140]; and lower neuronal dopamine-immunopositivity in the hypothalamus.[141]

12. Clinical context

Since complete statistics relating to all deaths-in-custody are not available in the public domain,[142] research in this area may be problematic. Hall[143] emphasized the importance of placing potential risks of ECD usage during law-enforcement activities into proper perspective with other alternatives. She suggested that collection of data related to such use should take precedence over studies of animal models or healthy human subjects.

Notwithstanding results of animal experiments with direct effects on the heart in some specific conditions of TASER ECD applications (e.g., Valentino et al.[45]), the likelihood of ventricular VF *directly* due to such devices has been reported to be extremely low during typical fatality cases involving excited delirium.[144] In one study of deaths-in-custody between 1990 and 2004, only one out of 45 cases involved use of an ECD.[145] In a prospective multicenter cohort study of 1201 subjects exposed to ECDs, two deaths-in-custody occurred; both were determined to be unrelated to ECD use.[146] In contrast, on the basis of some analyses, as many as 75% of excited delirium patients die at scene or during transport (C. Hall, quoted in Calgary Police Commission[147]). Bozeman and Winslow[148] concluded that drugs and/or restraint may be more important factors leading to death than several short exposures to ECDs. In 2006, it was estimated that as many as 800 people die from excited delirium each year.[149] Since different terminology and definitions of excited delirium may be used by different medical examiners, there are no reliable figures nationwide of suspects who died from the syndrome. One investigator estimated an in-custody death occurrence approximately every 2.5 days in the United States, with ECDs used on these subjects about 27% of the time.[150]

The very group of potential subjects exposed to ECDs that may be the most important, in terms of susceptibility to death (i.e., those exhibiting excited delirium), cannot be studied ethically in controlled experiments. Studies of volunteers might not be directly extrapolatable to law-enforcement situations with excited delirium or restraint of subjects.[151] This factor is a challenge in terms of potential research project design. Whether more extensive videotaping, etc., during law-enforcement use of ECDs will greatly improve our understanding is unknown.

Grant et al.[152] noted, "relevant data on the length of time an individual was in custody before death occurred were not consistently available." The length of time from ECD applications until death has varied from minutes to days. Gill[73] remarked that ECDs "certainly cause pain and stress." It could be reasonable, regarding individuals with advanced heart disease, to consider these external stressors, along with the time sequence of events and other circumstances. It may not be possible, however, to either prove or refute applications of an ECD as a direct cause of death in a subject exhibiting excited delirium.[72]

Relationships between excited delirium and other events occurring during deaths-in-custody (e.g., manual restraint and oleoresin capsicum) are beyond the scope of this paper, but have been reviewed previously by other investigators.[153–154] (Use of a new term, "cardiac dysrhythmia during restraint," was recently suggested as "the most intellectually honest cause of death in some challenging cases" of deaths-in-custody.[155])

As noted previously, "it is possible that there are no unique features of TASER ECD applications, in terms of physiological effects, other than the extreme degrees of muscle contraction (either repeated or long-duration) that may be achieved."[22]

13. Conclusions

Differences between changes in factors due to excited delirium versus those of ECD applications are not readily apparent in most cases. These factors include: direct and indirect effects of the cardiovascular system, respiration, rhabdomyolysis and muscle enzymes, hyperkalemia, acidosis, hyperglycemia, and increased hematocrit. On the basis of this review, however, more complete examination of pathological changes due to hyperthermia (which is present during excited delirium, but not during ECD exposures) may be useful to distinguish between the two different entities. Despite the potential value of this approach, deaths-in-custody may not be solely due to either of these events by themselves, but must always be considered in the context of all possible interacting factors.

Conflict of interest

The author has not had any relationship with any manufacturers of electronic control devices, including employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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